

Claims:

59

1. A non-slow-binding thrombin inhibitor of the formula:

A-B-C-Lys-D

5 wherein

A is H, 2-hydroxy-3-cyclohexyl-propionyl-, R_1 , R_1 -O-CO-, R_1 -CO-, R_1 -SO₂-, $-(CHR_2)_nCOOR_3$, or an N-protecting group, wherein

R_1 is selected from $-(1-6C)alkylene-COOH$, $(1-12C)alkyl$, $(2-12C)alkenyl$, $(6-14C)aryl$, $(7-15C)aralkyl$ and $(8-16C)aralkenyl$, the aryl group of which may be substituted with $(1-6C)alkyl$, $(2-12C)alkoxy$, hydroxy, or halogen;

R_2 is H or has the same meaning as R_1 ;

R_3 is selected from H, $(1-12C)alkyl$, $(2-12C)alkenyl$, $(6-14C)aryl$, $(7-15C)aralkyl$ and $(8-16C)aralkenyl$, the aryl group of which may be substituted with $(1-6C)alkyl$, $(2-12C)alkoxy$, hydroxy, or halogen;

n is an integer of 1 to 3;

B is a bond, L-Asp or an ester derivative thereof, Leu, norLeu, $-N(benzyl)-CH_2-CO-$, $-N(2-indane)-CH_2-CO-$, D-1-Piq, D-3-Piq, D-Tiq, Atc or a D-amino acid having a hydrophobic aromatic side chain;

C is Azt, Pro, Pec, norLeu(cyclo)Gly, an amino acid of one of the formulae $-N[(3-8C)cycloalkyl]-CH_2-CO-$ or $-N(benzyl)-CH_2-CO-$;

D is selected from COOH, tetrazole, oxazole, thiazole and benzothiazole;

or A and C have the aforesaid meanings, B is D-(3-8C)cycloalkylalanine, and D is tetrazole, oxazole, thiazole or benzothiazole;

or a prodrug thereof;

or a pharmaceutically acceptable salt thereof;

with the exception of the compound Me-D-Phe-Pro-Lys-COOH.

2. The non-slow-binding thrombin inhibitor of claim 1 wherein D is COOH.

3. The non-slow-binding thrombin inhibitor of claim 2 wherein A is H, $(1-12C)alkyl$, $-CO-(7-15C)aralkyl$, $-SO_2-(1-12C)alkyl$, $-SO_2-(6-14C)aryl$, or $-SO_2-(7-15C)aralkyl$; B is a bond, L-Asp, norLeu, D-1-Piq, or D-Phe; and C is Pro, norLeu(cyclo)Gly, or $-N(cyclopentyl)-CH_2-CO-$.

4. The non-slow-binding thrombin inhibitor of claim 3, wherein A is -SO₂-benzyl, B is a bond, and C is norLeu(cyclo)Gly, or wherein A is -SO₂-ethyl, B is D-Phe, and C is Pro; or wherein A is hydrogen, B is D-1-Piq, and C is Pro.

5. The non-slow-binding thrombin inhibitor of claim 1, wherein D is oxazole or thiazole.

6. The non-slow-binding thrombin inhibitor of claim 5, wherein A is H, (1-12C)alkyl, 2-hydroxy-3-cyclohexyl-propionyl-, -CO-(7-15C)aralkyl, -CO-(CH₂)_nCOOH, -SO₂-(6-14C)aryl, -SO₂-(7-15C)aralkyl, -SO₂-(1-12C)alkyl, -(CHR₂)_nCOOR₃, R₂ being H or (1-12C)alkyl and R₃ being H, (1-12C)alkyl or benzyl; and C is Pro, norLeu(cyclo)Gly, or -N[(3-8C)cycloalkyl]-CH₂-CO-.

7. A process for preparing a non-slow-binding thrombin inhibitor of claim 1, the process including coupling suitably protected amino acids or amino acid analogs, followed by removing the protecting groups.

8. A pharmaceutical composition comprising the non-slow-binding thrombin inhibitor of any one of claims 1-6 and pharmaceutically acceptable auxiliaries.

9. The non-slow-binding thrombin inhibitor of any one of claims 1-6 for use in therapy.

10. Use of the non-slow-binding thrombin inhibitor of any one of claims 1-6 for the manufacture of an antithrombotic medicament.